



Patent

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## AMENDMENTS

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## IN THE SPECIFICATION:

Please amend the specification to read as follows:

Page 14, line 4

D 1 The terms "alkylthio-" and "alkthio-" refer to the groups alkyl-S-.

Page 20, lines 16-21

D 2 The term "enhanced oral bioavailability" refers to an increase of at least 50% of the absorption of the dose of the parent drug or prodrug (not of this invention) from the gastrointestinal tract. More preferably it is at least 100%. Measurement of oral bioavailability usually refers to measurements of the prodrug, drug, or drug metabolite in blood, tissues, or urine following oral administration compared to measurements following systemic administration.

Page 25, line 30- page 26, line 12

D 3 Compounds of the formula M-P(O)(NHR<sup>6</sup>)O<sup>-</sup> are useful compounds for binding to nucleotide binding sites, such as AMP-binding sites, and certain sites known to recognize negatively charged compounds, e.g. carboxylic and phosphinic acids. Enzymes that catalyze the addition of water to a carbonyl compound, specifically a peptide carbonyl, an ester, a ketone or an aldehyde, are of particular interest since these enzymes recognized compounds that are tetrahedral and contain a negatively charged oxygen. An example is the zinc metalloproteinase class of enzymes which add water across a peptide carbonyl using a zinc-assisted catalytic mechanism. These enzymes are inhibited by phosphoramidates, e.g. NEP 24.11 is inhibited by the natural product Phosphoramidon. The prodrug strategy can provide a useful means for delivery of these compounds orally, or delivery of certain compounds to the liver in order to achieve greater efficacy or a greater therapeutic window. Enzyme inhibitors that may be suitable for delivery as prodrugs include certain phosphoramidates that inhibit NEP24.11, collagenase, stromolysin, gelatinase, ACE, endothelin converting enzyme, and metalloproteinases involved in matrix remodeling such as occurs in Rheumatoid arthritis and osteoarthritis and in the heart following an acute myocardial infarction, and tumor metastasis.

Page 35, lines 7-13

D 4 Another common toxicity associated with phosphonic acid drugs is gastrointestinal toxicity via in some cases GI erosions. Prodrugs of the current invention can decrease GI toxicities, especially toxicities produced by direct action of the drug on the GI tract after oral administration. Similar to the kidney, gut epithelial cells have organic anion transporters which can result in high intracellular drug levels and cytotoxicity. Since the negatively charged phosph(on)ate is not revealed until after absorption and cleavage in the liver, prodrugs of this invention reduce gut toxicity.